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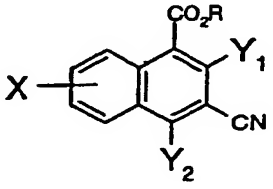
(54) Title: A PROCESS FOR THE PREPARATION OF 3-CYANO-1-NAPHTHOIC ACID AND SOME ANALOGUES THEREOF



(1)

(57) Abstract: The present invention is related to a process for the preparation of 3-cyano-1-naphthoic acid and some analogues thereof of formula (1), the intermediate 1-halo-3-cyano naphthalene and some analogues thereof used in this process and a process for the preparation of said intermediate.

A PROCESS FOR THE PREPARATION OF 3-CYANO-1- NAPHTHOIC ACID AND SOME ANALOGUES THEREOF

FIELD OF THE INVENTION

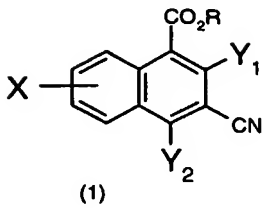
The present invention is related to a process for the preparation of 3-cyano-1- naphthoic acid and some analogues thereof, the intermediate 1-halo-3-cyano naphthalene and some analogues thereof used in this process and a process for the preparation of said intermediate.

BACKGROUND OF THE INVENTION

The compound 3-cyano-1- naphthoic acid is previously described in Jeffrey S. Albert et al; "Design, Synthesis, and SAR of Tachykinin Antagonist Activity", J. Med. Chem, Vol.45, no.18, 2002, p.3972-3983, p.3973 Scheme 2; p.3980-3981, no 18-20, Richtzenhain Hermann et al: "Substitution reactions with metallooorganic compounds. IV. The Grignardization of methoxyl-containing aromatic nitriles"; STN International, File CASREACT, Accession no. 44:10012, & Chem. Ber (1949), 82, 408-17, WO 01/77069, WO 00/59873, WO 00/20003, WO 00/20389, WO 02/12168, WO 01/77089 and WO 00/02859 and a process for the preparation of the same is previously described in Jeffrey S. Albert et al; "Design, Synthesis, and SAR of Tachykinin Antagonist Activity", J. Med. Chem, Vol.45, no.18, 2002, p.3972-3983, p.3973 Scheme 2; p.3980-3981, no 18-20, WO 01/77069, WO 00/59873, WO 00/20003, WO 00/20389, WO 02/12168 and WO 01/77089. This process is unattractive for commercial manufacture on account of toxic process effluent arising from use of mercury salt to achieve regioselective decarboxylation, low through process yield and operationally unattractive bromination in concentrated nitric acid.

BRIEF DESCRIPTION OF THE INVENTION

The present invention refers to a process for preparing the compound of formula (1)

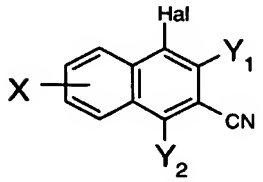


(1)

wherein X and/or Y_1 and/or Y_2 are independently H, cyano, nitro, trifluoromethoxy, trifluoromethyl, alkoxy, or alkyl and R is H or alkyl

either

a) in the case where R=H, by metallo-dehalogenation followed by carboxylation of a compound of formula (12)

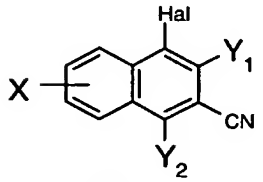


(12)

wherein X, Y_1 and Y_2 are as defined above, and Hal is Br, I or Cl

or

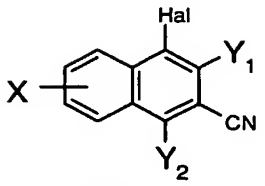
b) in the case where R=H or alkyl, by palladium mediated carbonylation of a compound of formula (12)



(12)

with the proviso that the compound 1-iodo-3-cyano-2-methoxynaphthalene is excluded, followed by solvolysis.

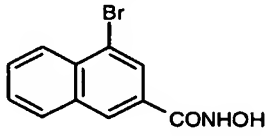
Furthermore the present invention refers to a compound of formula (12)



(12)

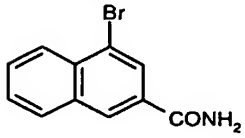
wherein X and/or Y_1 and/or Y_2 are independently H, cyano, nitro, trifluoromethoxy, trifluoromethyl, alkoxy, or alkyl and Hal is Br, I or Cl, which is a compound not previously described and which is a key intermediate in the preparation of the compound of formula (1, R=X= Y_1=Y_2 =H) and moreover to a process for preparing a compound of formula (12, Y_1=Y_2=X=H).

Moreover the present invention refers to some other intermediates that may be used in the process for preparing the compound of formula (1, R=X= Y_1=Y_2 =H), namely the compound of formula (20)



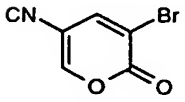
(20)

the compound of formula (18)



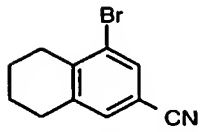
(18)

3-bromo-5-coumalonitrile (27)



(27)

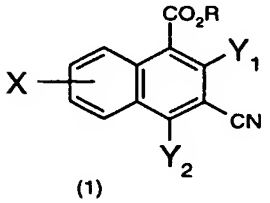
and the compound of formula (63)



(63)

DETAILED DESCRIPTION OF THE INVENTION

The process for preparing the compound of formula (1)

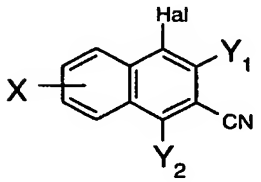


(1)

wherein X and/or Y_1 and/or Y_2 are independently H, cyano, nitro, trifluoromethoxy, trifluoromethyl, alkoxy, or alkyl and R is H or alkyl

is carried out either

a) (in the case where R=H) by metallo-dehalogenation followed by carboxylation of a compound of formula (12)

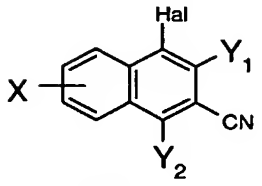


(12)

wherein X, Y_1 and Y_2 are as defined above, and Hal is Br, I or Cl

or

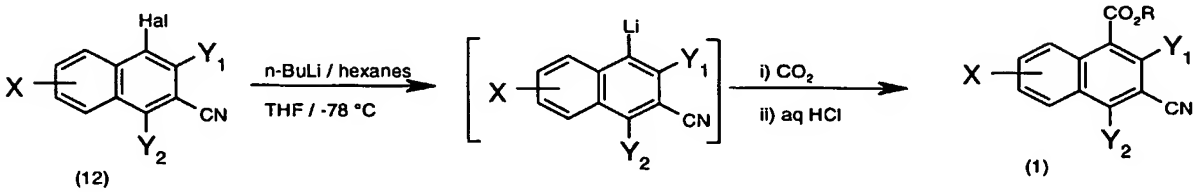
b) (in the case where R=H or alkyl) by palladium mediated carbonylation of a compound of formula (12)



(12)

with the proviso that the compound 1-iodo-3-cyano-2-methoxynaphthalene is excluded, followed by solvolysis.

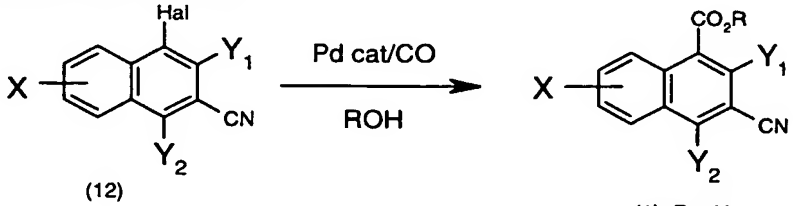
Metallo-dehalogenation and carboxylation of compound of formula (12)



(12) (1)

Metallo-dehalogenation and carboxylation may be carried out by treatment of compound (12) with alkyl-lithium reagent, e.g. ^{n}BuLi, in THF alone or in admixture with solvents like hexane at a temperature below –10 °C, and preferably between -30°C and -75°C, followed by reaction of the lithiated intermediate with CO_2 and subsequent acidification with e.g. HCl.

Palladium mediated carbonylation



(12)

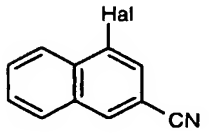
(1) R = H

(6) R = Me

The halo-cyano-naphthalene (12) may be reacted with carbon monoxide under elevated pressure, for example between 5 bar and 100 bar, in a solvent such as methanol with an

organic base such as triethylamine catalysed by palladium with or without additional phosphine ligand such as triphenyl phosphine or bis-diphenylphosphino propane. The active palladium catalyst can be generated *in situ* from palladium salts such as palladium (II) chloride or palladium bis(triphenylphosphine)palladium(II) chloride. The product (1) may be isolated by first of all removing solid residues by filtration and then extracting into aqueous and back into organic with pH control, followed by crystallisation from toluene. The product (6) may be isolated by removing solid residues by filtration followed by crystallisation from solvent.

The process for preparing the compound of formula (12, Y_1=Y_2=X=H)



(12, Y_1=Y_2=X=H)

wherein Hal is Br, I or Cl

may be carried out by any of the following routes:

(i)

by

(a) treating malic acid (7) with oleum or alternative strongly acid dehydrating media to give coumalic acid (8);

(b) esterifying coumalic acid (8) to give a pyrone ester (9);

(c) brominating the pyrone ester (9) to give a 3-bromo coumalic ester (10);

(d) reacting the 3-bromo coumalic ester (10) with *in situ* generated benzyne followed by decarboxylation to give a bromonaphthoate (11); and

(e) converting/transforming the bromonaphthoate (11) to 1-bromo-3-cyano naphthalene (12, Y_1=Y_2=X=H)

or (ii)

by

(a) treating malic acid (7) with oleum or alternative strongly acid dehydrating media to give coumalic acid (8);

(b) converting coumalic acid (8) into coumalonitrile (25) and subsequently brominating to give 3-bromo-5-coumalonitrile (27); and then

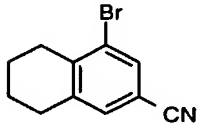
(c) converting 3-bromo-5-coumalonitrile (27) into 1-bromo-3-cyano naphthalene (12, $Y_1=Y_2=X=H$)

by cycloaddition of *in situ* generated benzyne, followed by subsequent decarboxylation

or (iii)

by

1a) cyanation of 1,2,3,4-tetrahydronaphthalene followed by bromination to give the compound of formula (63)



(63)

or

1b) bromination of 1,2,3,4-tetrahydronaphthalene followed by cyanodebromination, followed by bromination to give the compound of formula (63); or

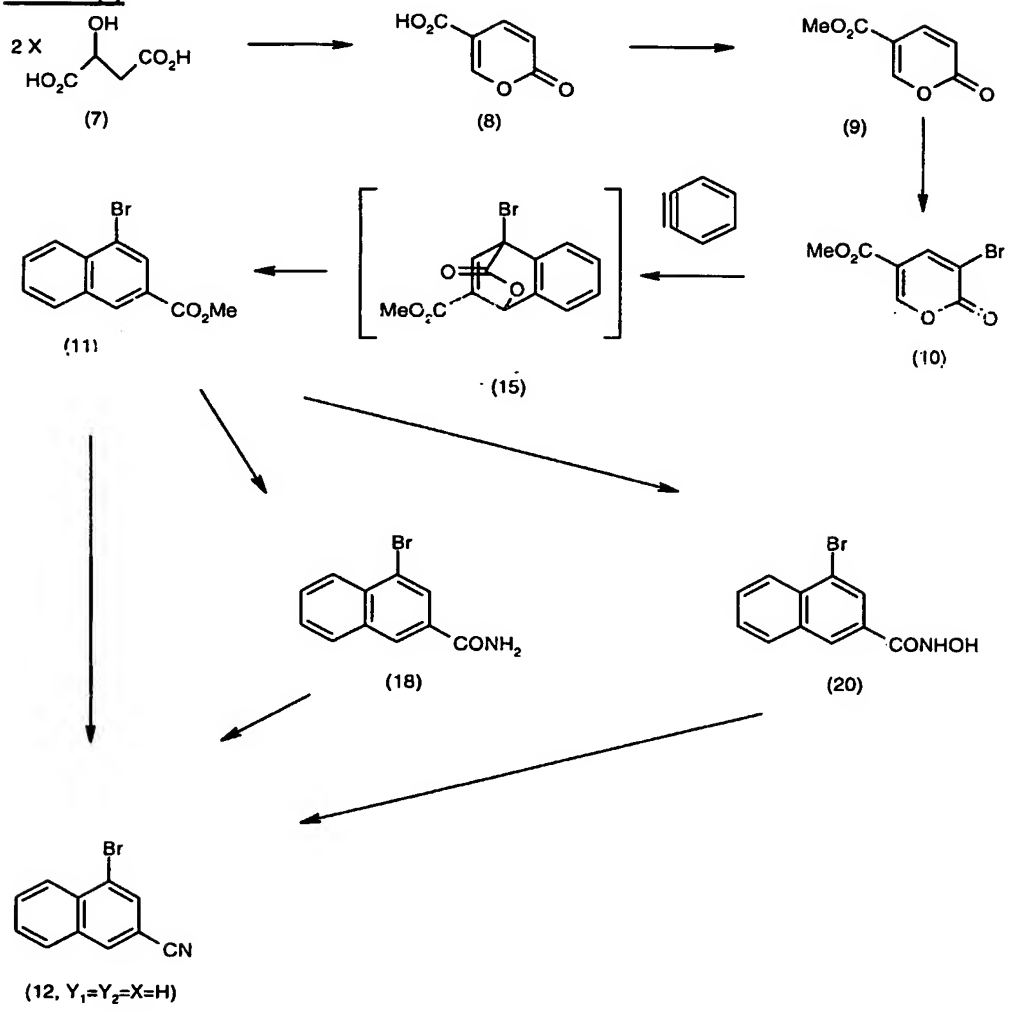
1c) bromination of 1,2,3,4-tetrahydronaphthalene followed by metallation and carboxylation followed by conversion to the 6-cyano-1,2,3,4-tetrahydronaphthalene followed by bromination to give the compound of formula (63);

followed by

2) oxidative aromatization of the compound of formula (63) into 1-bromo-3-cyano naphthalene (12, Y_1=Y_2=X=H);

which are illustrated in the reaction schemes below.

Route (i)



Stage (a) - Coumalic acid:

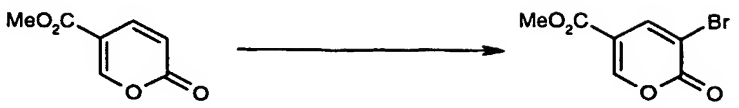
Oleum or alternative strongly acid dehydrating media is added to a suspension of malic acid in a strong acid e.g. H_2SO_4 at about 50°C to 90°C, preferably at 75°C to 85°C. Then the mixture is cooled and the product coumalic acid is filtered off.

Coumalic acid (8) is also commercially available.

Stage (b) - Pyrone Ester:

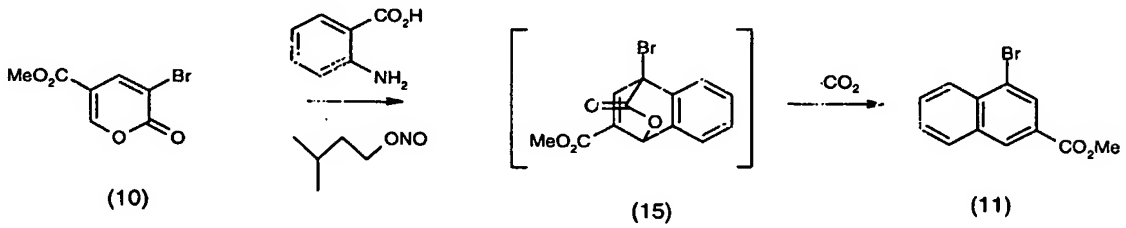
Diisopropylethylamine or other non-nucleophilic base (e.g. DBU) is added to a suspension of coumalic acid in NMP, dimethylsulphate (or else MeBr or MeI) and a non-nucleophilic base, e.g. DBU or $^{i}Pr_2Net$, are added, and the reaction stirred at between 20°C and 30°C . The reaction mass is diluted, e.g. with toluene, and drowned out into water followed by washing of the organic phase with aqueous bicarbonate and finally water. The solvent is removed by evaporation *in vacuo* and the crude product pyrone ester is purified by filtration isolation from the residual mother liquors.

Stage (c) - 3-Bromo Coumalic Acid:



Pyrone ester is brominated, e.g. with pyridinium bromide perbromide (pyridinium tribromide) or Br_2 in glacial acetic acid to give 3-bromo coumalic acid .

Stage (d) - Bromonaphthoate:

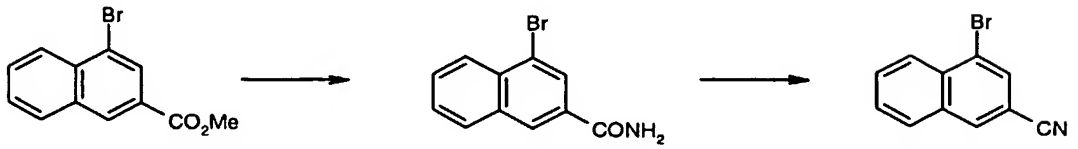


Isoamyl nitrite and a solution of anthranilic acid in e.g. ethylene glycol dimethyl ether are added to a refluxing solution of a 3-bromo coumalic ester in e.g. ethylene glycol dimethyl ether in the presence of an acid, e.g. catalytic trichloroacetic acid . Benzene-2-diazonium carboxylate is formed by anthranilic acid diazotisation followed by *in situ* decomposition to give benzyne. The reactive benzyne undergoes [4+2] cycloaddition with the 3-bromo coumalic ester to give an intermediate (15), which then extrudes carbon dioxide to give the desired bromonaphthoate. Heating under reflux is continued, the reaction mass is then cooled to about 50°C, a solvent, e.g. toluene is added and the mixture then cooled to ambient. The solution is washed with dilute sodium hydroxide solution , sodium bisulphite solution, water , hydrochloric acid and water again. The solution is then concentrated *in vacuo* to give the crude bromonaphthoate product.

Stage (e) - 1-Bromo-3-Cyano naphthalene :

Three methods for this transformation are possible:

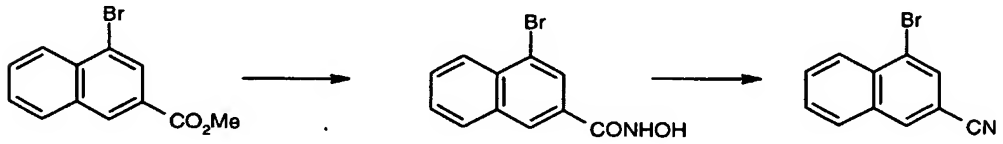
Method 1: Conversion to the amide (18) followed by dehydration



(11) (18) (12, $Y_1=Y_2=X=H$)

Bromonaphthoate (11) is heated with ammonia in the presence of a solvent, e.g. toluene, and a catalyst, e.g. KI, at a high temperature to give bromoamide (18)
This is followed by dehydration by heating the bromoamide in a large excess of a dehydrating agent, e.g. $SOCl_2$, to give the compound of formula (12).

Method 2: Conversion to the hydroxamic acid (20)

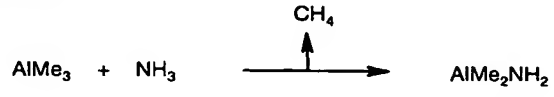


(11) (20) (12, $Y_1=Y_2=X=H$)

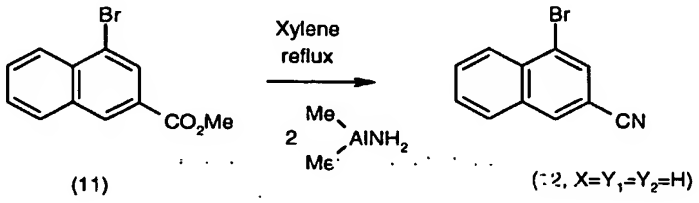
Preparation of hydroxamic acid (20) is achieved by reaction of a bromonaphthoate (11) with hydroxylamine, or a salt thereof, e.g. hydrochloride plus added base. Conversion of the hydroxamic acid (20) to 1-bromo-3-cyano naphthalene (12) is effected by dehydration, e.g. by treatment with PBr_3.

Method 3: Direct conversion of Bromonaphthoate (11) to 1-bromo-3-cyano naphthalene (12, $X=Y_1=Y_2=H$) with Me_2AlNH_2 (21).

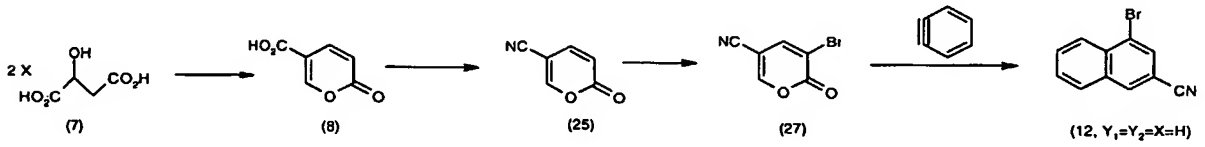
The reagent for this transformation, dimethylaluminium amide, is prepared under strictly anhydrous conditions in an inert atmosphere by condensing anhydrous NH_3 into a solution of $AlMe_3$ at low temperature.



A solution of Me_2AlNH_2 solution is added to a solution of a bromonaphthoate in a high-boiling solvent, e.g. m-xylene, and the mixture is heated to reflux. Rapid conversion to the 1-bromo-3-cyano naphthalene (12) occurs and the product is isolated.



Route (ii)



Stage (a) - Coumalic acid: See Route (i) Stage (a) above

Stage (b) - 3-bromo-5-coumalonitrile

Coumalic acid (8) is converted to the corresponding nitrile (25) by conversion to the acid chloride (28) by reaction with a chlorinating agent, e.g. thionyl chloride, followed by reaction with sulfamide ($H_2NSO_2NH_2$).

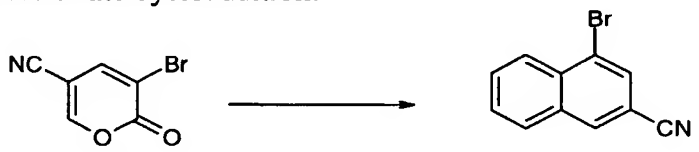
Coumalonitrile (25) is brominated using a brominating agent, e.g. pyridinium bromide perbromide (PBPB) in a high-boiling solvent to give bromocoumalonitrile (27). The product is isolated from unreacted starting material by crystallisation.

(25) (27)

Stage (c) - 1-Bromo-3-Cyano naphthalene

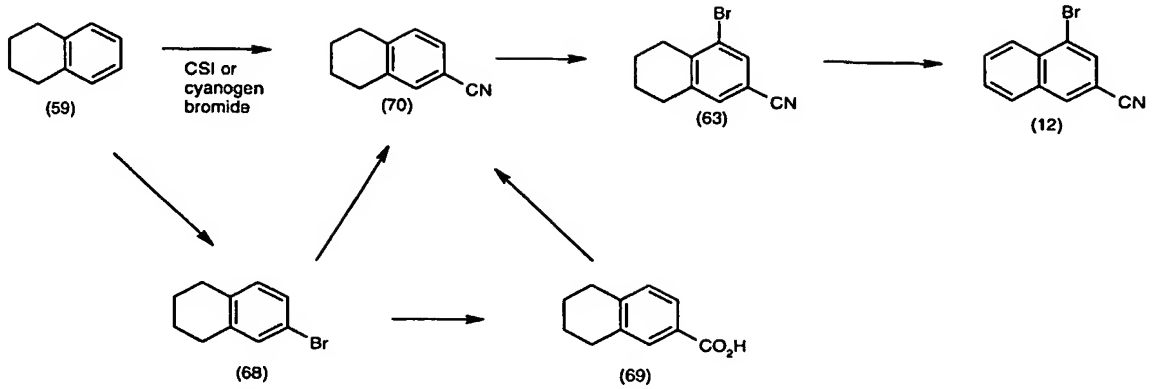
Compound (27) is converted into compound (12) by cycloaddition of *in situ* generated benzyne, followed by subsequent decarboxylation e.g. by heating.

The presence of a cyano- rather than an ester group at the 5- position of pyrone ring does not affect the progress of the cycloaddition.



(27) (12)

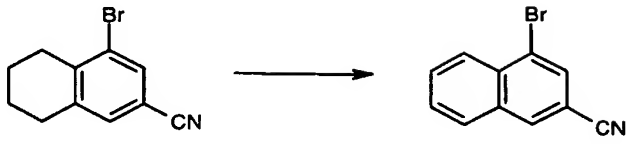
Route (iii)



1,2,3,4-tetrahydronaphthalene (also known as Tetralin ®) is cyanated to give cyanotetrahydronaphthalene (70), either directly by reaction with cyanogen bromide with aluminium chloride as catalyst in carbon disulphide, or via bromotetrahydronaphthalene (68), the resulting cyano tetrahydronaphthalene (70) is brominated to give bromocyanotetrahydronaphthalene (63) which is converted to bromocyanonaphthalene (12) by oxidative aromatisation.

Thus, tetrahydronaphthalene (59) is reacted with bromine, with added iodine as catalyst, the 6-bromo-1,2,3,4-tetrahydronaphthalene (plus regioisomers) is either a) cyanated by reaction with copper (I) cyanide in NMP at 130 °C for 48h to give 6-cyano-1,2,3,4-tetrahydronaphthalene (70) or b) is lithiated by reaction with n-butyl lithium in THF at –78 °C followed by reaction with carbon dioxide and then dilute hydrochloric acid to furnish 5,6,7,8-tetrahydronaphthalene-2-carboxylic acid (69) along with its regioisomer from which tetrahydronaphthalene acid (69) is purified by repeated recrystallisation. This acid is converted to cyanonaphthalene (70) by conversion to acid chloride by reaction with thionyl chloride with a small amount of NMP as catalyst, followed by conversion to amide by reaction with ammonia, followed by amide dehydration, for example with PBr_3. 5,6,7,8-Tetrahydronaphthalene-2-carbonitrile (70) is brominated by reaction with bromine with catalytic ferric bromide in carbon tetrachloride to give bromonitrile (63).

Aromatisation of Substituted Tetralins



(63) (12)

The aromatisation of the compound of formula (63) into the compound of formula (12) is carried out by heating the compound of formula (63) at a high temperature in the presence of a metal catalyst, e.g. Pd/C. Alternatively, the aromatisation may be carried out for example by stirring with elemental sulphur in a solvent at ambient temperature.

PREPARATIONS

Preparation 1

Conversion of malic acid to coumalic acid Oleum (287g) is added dropwise over 2h to a suspension of malic acid (200g) in concentrated H_2SO_4 (313g) at 75°C and the resulting solution stirred for a further 4h, maintaining temperature at 75°C throughout. The mixture is cooled and then drowned out into ice-cold water over 1h. After stirring for 15min and standing overnight, the mixture is cooled to below 10°C and the product is isolated by filtration to give coumalic acid (71 g, 95% purity, 65% yield) after washing and drying.

Preparation 2

Conversion of coumalic acid to coumalic acid, methyl ester Diisopropylethylamine is added to a suspension of coumalic acid (115.5g) in N-methylpyrrolidone (600mL) at 25°C, dimethylsulphate (100.9g) is added over 1h and the reaction stirred at 25°C for 2h. The reaction mass is diluted with toluene, and extracted with water then bicarbonate and finally water. The toluene is removed *in vacuo* and the crude product pyrone ester is purified either by short path distillation or by crystallisation and trituration to give (after removal of

residual solvent by evaporation *in vacuo)* the coumalic acid methyl ester (78.8g, 99% purity, 64% yield).

Preparation 3

Conversion of coumalic acid, methyl ester to 3-bromocoumalic acid, methyl ester A solution of pyrone ester (39g, 95% purity) in acetic acid is added over 3.5hr to a refluxing solution of pyridinium tribromide (105g) in glacial acetic acid (233g). The mixture is held at reflux (85°C -> 107°C) for 3hr then cooled to ambient. Water is added and the crude product is isolated by filtration then washed with water. The crude product is purified by recrystallisation from toluene and *iso*-hexane to give 3-bromocoumalic acid, methyl ester (46g, 82% yield).

Preparation 4

Conversion of 3-bromocoumalic acid, methyl ester to methyl 4-bromo-2-naphthoate

Isoamyl nitrite (24.2g) and a solution of anthranilic acid (28.0g) in ethylene glycol dimethyl ether (90g) are added over 3h to a refluxing solution of 3-bromo coumalic acid, methyl ester (23.3g) in ethylene glycol dimethyl ether (135.8g) in the presence of catalytic trichloroacetic acid (0.165g). The reaction is refluxed for a further 1 hr after the end of addition to ensure complete reaction. The reaction mass is cooled to 50°C, toluene (279g) is added and the mixture then cooled to ambient. The toluene solution is washed with sodium hydroxide solution (75mL, 2M), sodium bisulphite solution(75mL, 5%), water (75mL), hydrochloric acid and water again. The toluene solution is then concentrated *in vacuo* to give methyl 4-bromo-2-naphthoate (30g, 85% purity, 93% yield)..

Preparation 5

Conversion of methyl 4-bromo-2-naphthoate to 4-bromo-2-naphthonitrile

Dimethylaluminium amide is prepared by the reaction of a solution of trimethylaluminium in toluene (150mL, 2M) with excess anhydrous ammonia (25.5g) at -78°C. Excess ammonia is removed by evaporation at 110 °C and the dimethylaluminium amide solution is then charged to a solution of the bromonaphthoate (39.8g) in m-xylene (321.7g) at

110°C over 1hour.The reaction is held at 110°C for a further hour and then rapidly cooled to room temperature in ice. The reaction mass is drowned out into aqueous HCl (750 mL, 2M) over 1.5 hours at 5-10°C. The *m*-xylene solution is concentrated *in vacuo* to give the crude product, which is recrystallised from toluene/*iso*-hexane to give 4-bromo-2-naphthonitrile (18.9 g, 54% yield).

Preparation 6

Conversion of methyl 4-bromo-2-naphthoate to 4-bromo-2-naphthonitrile *via* 4-bromo-2-naphthamide To a Carius tube equipped with small magnetic flea and protective outer metal casing is charged methyl 4-bromo-2-naphthoate (1.18 g), aqueous ammonia (9 ml), potassium iodide (0.075 g) and methanol (2 ml). The apparatus is assembled, and lowered into an oil bath at 130 °C. The pressure rises to 4.25 bar. The mixture is heated with stirring under these conditions for 66 h, after which time the assembly is removed from the oil bath and allowed to cool to ambient temperature/pressure. The mixture is cooled to 0 °C to complete crystallisation, and filtered to remove the product. The product is dissolved in EtOAc (50 ml) and washed with 10 % w/v aqueous Na_2CO_3 (2 x 10 ml). The organic layer is separated, dried ($MgSO_4$) and the solvent removed *in vacuo* to give the product 4-bromo-2-naphthamide as colourless prisms (0.38 g, 94 % str by GC area, 33 % yield,).

To a 10 ml 1-necked round-bottomed flask equipped with magnetic stirrer, condenser and inert atmosphere is charged 4-bromo-2-naphthamide (0.093 g) and thionyl chloride (2 ml). The mixture is heated under reflux for 18 h, and the excess thionyl chloride is removed *in vacuo* to afford the crude product 4-bromo-2-naphthonitrile as a yellow solid.

^{1}H nmr ($CDCl_3$): 8.15 (s, 1H, ArH), 8.24 (d, 1H, J = 7.4 Hz, ArH), 7.90-7.62 (m, 4H, ArH).

MS: 233 (M^+), 231 (M^+), 152, 125, 76.

Preparation 7

Conversion of methyl 4-bromo-2-naphthoate to 4-bromo-2-naphthonitrile *via* 4-bromo-*N*-hydroxy-2-naphthamide

To a 100 ml 2-necked round-bottomed flask equipped with magnetic stirrer, graduated pressure equalised dropping funnel and inert atmosphere is charged bromonaphthoate (2.69 g), hydroxylamine hydrochloride (2.78 g) and methanol (16 ml). 5 M Methanolic KOH (10 ml.) is added dropwise over 40 min to the vigorously stirred suspension at room temperature. An exotherm and an orange colouration is noted on each addition. The reaction mixture (beige suspension) is stirred at room temperature for 17 h after addition of base. The reaction mixture is concentrated to ca. half volume *in vacuo* (water bath < 45 °C) and a 1:1 mixture of water/glacial acetic acid (50 ml) added with vigorous stirring. Stirring is continued for 40 min, and a further portion of 1:1 water/glacial acetic acid (20 ml) added when the suspension becomes too thick to stir. Stirring is continued for 1 h, and the product filtered off under reduced pressure and washed with cold water (3 x 15 ml). The product hydroxamic acid is dried in the vacuum oven at 70 °C to give 4-bromo-*N*-hydroxy-2-naphthamide as a beige powder (2.2 g, 76 % str. by LC area, 76 % yield,).

To an oven dried 250 ml 2-necked round-bottomed flask equipped with magnetic stirrer, condenser, septum and inert atmosphere is charged 4-bromo-*N*-hydroxy-2-naphthamide (2.0 g) and fluorobenzene (80 ml). Phosphorous tribromide (1.8 ml) is added dropwise over 10 min to the stirred suspension at room temperature and the mixture heated to reflux (85 °C) whereupon a clear orange solution is obtained. Reflux is continued for 18 h, and the solution allowed to cool. The crude reaction mixture is poured into saturated aqueous $NaHCO_3$ solution (50 ml) and the product extracted with toluene (3 x 50 ml). The combined organic extracts are washed with brine (50 ml) and the solvent removed *in vacuo*. The residue is crystallised from methanol to give the product 4-bromo-2-naphthonitrile as pale yellow prisms (0.73 g)

The ^1H nmr and mass spectra of the above end product corresponds to those previously obtained.

Preparation 8

Conversion of coumalic acid to 3-bromo-2-oxo-*2H*-pyran-5-carbonitrile (3-bromocoumalonitrile) *via* 2-oxo-*2H*-pyran-5-carbonitrile (coumalonitrile)

Coumalic acid (3.91 g) and thionyl chloride (31 ml) are charged to a 100 ml 2-neck round bottomed flask equipped with condenser, magnetic stirrer and inert atmosphere, and the suspension heated to reflux for 1 h. The clear yellow solution is allowed to cool, and the excess thionyl chloride removed *in vacuo*. Sulfamide (3.22 g) is added, and the solid mixture heated to 120°C (bath temp.) for 1 h. The acid chloride melts after a few seconds, and HCl is vigorously evolved. After ca. 15 min, a red foam is obtained, which on further heating collapses to a dark red viscous oil. After 1 h, the reaction mixture has solidified. The reaction mixture is allowed to cool, and transferred to a separating funnel with 10 % w/v aqueous $NaHCO_3$ solution (150 ml) (heating with the latter being necessary to remove the crude product from the flask). The product is extracted with CH_2Cl_2 (2 x 50 ml) and the combined organic layers washed with sat. NaCl solution (100 ml). The extracts are dried ($MgSO_4$) and the solvent removed *in vacuo*. The residue is purified by crystallisation from MeOH (2 ml) at 0°C. The product coumalonitrile is obtained as dark orange prisms (1.7 g).Coumalonitrile (2.0g), pyridinum bromide perbromide (5.28g), dimethoxy ethane (13g) and toluene (12,98) are charged to a 100 ml 2-neck round bottomed flask equipped with condenser, magnetic stirrer and inert atmosphere, and heated under reflux for 4 h. The reaction mixture is poured into water (100 ml) and extracted with CH_2Cl_2 (3 x 100 ml). The extracts are dried ($MgSO_4$) and the solvent removed *in vacuo*. The residue is swirled with ether (20 ml) and the extracts decanted off. The residue is purified by crystallisation from acetone to give the 3-bromo-2-oxo-*2H*-pyran-5-carbonitrile as an orange powder (1.25 g, 81 % str. by LC area, 31 % yield)

^{1}H nmr ($CDCl_3$): 7.74 (d, 1H, J 2.5 Hz, H_a), 8.04 (d, 1H, J = 2.2 Hz, H_b).

MS: 201 (M^+), 199 (M^+), 173, 171, 144, 142, 120, 64, 29.

Preparation 9

Conversion of 3-bromo-2-oxo-2*H*-pyran-5-carbonitrile (3-bromocoumalonitrile) to 4-bromo-2-naphthonitrile Solutions of anthranilic acid(1.8 g, 12.8 mmol) in DME (10 ml) and isoamyl nitrite (1.54 g, 12.8 mmol) in DME (10 ml, 8.7 g) are added dropwise over 20 min to a stirred solution of 3-bromocoumalonitrile (1.15 g, 4.6 mmol) and trichloroacetic acid (0.047 g, 0.29 mmol) in DME (40 ml) held at reflux. The mixture is refluxed for a further 10 min, allowed to cool and poured into water (100 ml). The product is extracted with CH_2Cl_2 (2 x 50 ml) and the volatiles removed *in vacuo*. The product crystallises from the residual amyl alcohol at – 20°C and the dirty orange solid is collected by filtration *in vacuo*, and dried in the oven at 40°C to give 4-bromo-2-naphthonitrile (0.81 g, 49 % yield).

Preparation 10

Conversion of 1,2,3,4-Tetrahydronaphthalene to 5,6,7,8-tetrahydronaphthalene-2-carbonitrile

1,2,3,4-Tetrahydronaphthalene (3.3 g), aluminium chloride (6.7 g), cyanogen bromide (5.5 g) and carbon disulphide (70 ml) were heated together under reflux for 8 hours however this achieved negligible reaction, the mixture was accordingly concentrated by distilling out solvent at atmospheric pressure until the temperature of the reaction mixture rose to 60 °C. Stirring was continued at 60 °C for 8 hours, the mixture was cooled, chloroform (100 ml) was added and the resulting mixture then added slowly to a stirred mixture of concentrated hydrochloric acid (3 g) and 50:50 ice water (150 ml) at 0 °C. The resulting phases were separated, the aqueous layer was extracted with chloroform (2 x 100 ml), the combined organic phases were washed with saturated aqueous sodium bicarbonate solution (150 ml) and water (2 x 50 ml), they were dried ($MgSO_4$) and solvent removed by evaporation *in vacuo* to give crude product (3.8 g) comprising a 3:1 mixture of 5,6,7,8-tetrahydronaphthalene-2-carbonitrile and 5,6,7,8-tetrahydronaphthalene-1-carbonitrile. This was purified by distillation under reduced pressure to give 5,6,7,8-tetrahydronaphthalene-2-carbonitrile in 40% overall yield.

Conversion of 5,6,7,8-tetrahydronaphthalene-2-carbonitrile to 4-bromo-5,6,7,8-tetrahydronaphthalene-2-carbonitrile

Bromine (2.5 g, 15.6 mmol) was added cautiously to a stirred mixture of 5,6,7,8-tetrahydronaphthalene-2-carbonitrile (2 g, 12 mmol) and ferric bromide (4.7 g, 15.6 mmol) in carbon tetrachloride (20 ml) at 10 °C. The mixture was stirred at ambient temperature for 8 hours, it was worked up by adding to dilute aqueous hydrochloric acid and extracting with chloroform followed by removal of solvent by evaporation *in vacuo* to give the crude product as a brown oil (5.74 g, 45% purity by gc area, 86% yield). The product was purified by chromatography on silica gel using 1:9 ethyl acetate:hexane eluent to give 4-bromo-5,6,7,8-tetrahydronaphthalene-2-carbonitrile as a mixture of isomers.

Preparation 11

Conversion of 1,2,3,4-tetrahydronaphthalene to 5-bromo-1,2,3,4-tetrahydronaphthalene and 6-bromo-1,2,3,4-tetrahydronaphthalene

Bromine (66.1 g, 0.41 mol)) was added over 3 hours, with stirring at 5 °C to 10 °C, to the 1,2,3,4-tetrahydronaphthalene (50 g, 0.374 mol) along with a small piece of iodine (0.25 g, 0.98 mmol). Stirring was continued at ambient temperature for 6 hours and the mixture was then poured slowly into a stirred saturated aqueous solution of sodium sulphite (200 ml) at 10 °C. Stirring was continued for 15 minutes, the resulting mixture was extracted with methylene chloride (3 x 50 ml), the combined organic extracts were washed with water (200 ml), dried ($MgSO_4$) and solvent removed by evaporation *in vacuo* to give 5-bromo-1,2,3,4-tetrahydronaphthalene along with the 6-bromo-1,2,3,4-tetrahydronaphthalenec isomer (86 g, 89.7% purity of combined mono-brominated isomers present in *circa* 3:2 ratio, combined mono-bromo isomer yield 96%).

Conversion of 5-bromo-1,2,3,4-tetrahydronaphthalene and 6-bromo-1,2,3,4-tetrahydronaphthalene to 5,6,7,8-tetrahydronaphthalene-2-carbonitrile along with 5,6,7,8-tetrahydronaphthalene-1-carbonitrile isomer

A mixture of 5-bromo-1,2,3,4-tetrahydronaphthalene and 6-bromo-1,2,3,4-tetrahydronaphthalene (20 g), copper (I) cyanide (8.6 g) and anhydrous N-

methylpyrrolidinone (41.3 g) were stirred under dry nitrogen at 130 °C for 40 h. The mixture was cooled to ambient temperature, further N-methylpyrrolidinone (10 g) was added along with saturated aqueous brine (30 ml), the resulting mixture was stirred at ambient for 3 hours and filtered to remove solids. The filtrates were extracted with n-hexane (3 x 50 ml). The combined organic extracts were washed with water (100 ml), dried ($MgSO_4$) and evaporated *in vacuo* to give crude product (16.2 g). This was purified by distillation to give 5,6,7,8-tetrahydronaphthalene-2-carbonitrile along with regioisomer (13.2 g, 95% purity, 84% yield).

Preparation 12

Conversion of 5-bromo-1,2,3,4-tetrahydronaphthalene and 6-bromo-1,2,3,4-tetrahydronaphthalene to 5,6,7,8-tetrahydronaphthalene-1-carboxylic acid and 5,6,7,8-tetrahydronaphthalene-2-carboxylic acid

n-Butyl lithium (9.6 ml of 2.5M solution in hexane) was added dropwise over 30 minutes to a stirred solution of 5-bromo-1,2,3,4-tetrahydronaphthalene in mixture with its regioisomer 6-bromo-1,2,3,4-tetrahydronaphthalene (5 g) in dry THF (125 ml) and hexane (35 ml) at –70 °C, stirring was continued at –78 °C for 30 minutes, carbon dioxide gas was bubbled through the mixture at –70 °C until no further exotherm was evident, carbon dioxide gas addition was continued for a further 10 minutes as the reaction was allowed to warm to ambient temperature, the mixture was poured into 2M aqueous hydrochloric acid (100 ml) and the resulting mixture was extracted with diethyl ether (3 x 50 ml). The combined organic extracts were washed with water (100 ml) and were then extracted with 10% aqueous sodium carbonate solution (3 x 50 ml). The combined aqueous carbonate extracts were acidified carefully by addition of 2M hydrochloric acid to adjust the pH to pH 1. The resulting mixture was extracted with diethyl ether (3 x 50 ml), the combined organic extracts were washed with water (50 ml) and dried ($MgSO_4$) before solvent was removed by evaporation *in vacuo* to give the crude product in 64% yield comprising a mixture of regioisomers of 5,6,7,8-tetrahydronaphthalene carboxylic acid . This mixture was purified by repeated recrystallisation from ethyl acetate to give 5,6,7,8-tetrahydronaphthalene-2-carboxylic acid as crystallised solid in 93% purity along with

5,6,7,8-tetrahydronaphthalene-1-carboxylic acid as the major component present in the crystallisation mother liquors.

Conversion of 5,6,7,8-tetrahydronaphthalene-2-carboxylic acid to 5,6,7,8-tetrahydronaphthalene-2-carbonitrile

Acetyl chloride (5 g, 64 mmol) is added dropwise to dry methanol (150 ml) with stirring at ambient temperature under dry nitrogen. Stirring is continued for 15 minutes, 5,6,7,8-Tetrahydronaphthalene-2-carboxylic acid (1 g, 5.7 mmol) is added, the mixture is stirred at ambient temperature for 10 hours and solvent removed by evaporation *in vacuo* to give methyl 5,6,7,8-tetrahydronaphthalene-1-carboxylate. This is then converted to 5,6,7,8-tetrahydronaphthalene-2-carbonitrile using the same procedure described above for conversion of methyl 4-bromo-2-naphthoate to 4-bromo-2-naphthonitrile using dimethylaluminium amide.

Preparation 13 Conversion of 4-bromo-5,6,7,8-tetrahydronaphthalene-2-carbonitrile to 4-bromo-2-naphthonitrile

4-Bromo-5,6,7,8-tetrahydronaphthalene-2-carbonitrile (0.1 g) was heated with 10% palladium on carbon (1.65 g) under air at 200 °C to 210 °C for 22 hours to give crude 4-bromo-2-naphthonitrile as seen by gc (approximately 75% yield by gc area).

EXAMPLES

Example 1

Conversion of 4-bromo-2-naphthonitrile to 3-cyano-1-naphthoic acid *via* metallo-dehalogenation and carboxylation. To a 50 ml 4-neck round bottomed flask equipped with a magnetic stirrer, thermometer, septum, CO_2 inlet, N_2 inlet/bubbler and external dry ice/acetone cooling bath is charged (0.35 g, 1.25 mmol), anhydrous hexane (2 ml) and anhydrous THF (8 ml). The suspension is cooled to - 75 °C and BuLi (0.6 ml) added dropwise over 20 min to the vigorously stirred suspension. The bright red solution is stirred for a further 5 min and then carbon dioxide bubbled very slowly through the reaction mixture with external cooling. The quenching reaction is very exothermic -

maximum temperature reached is - 65 °C. Reaction is judged complete when no further temperature increase is observed upon addition of carbon dioxide. The mixture is stirred at - 65 °C for a further 10 min, and then added cautiously to 2 M HCl. The product is extracted with ethyl acetate (3 x 50 ml), the combined extracts dried ($MgSO_4$) and the solvent removed *in vacuo* to give 3-cyano-1-naphthoic acid (*circa* 20% yield).

^{1}H nmr (D_6DMSO): 7.69-7.87 (m, 2H, 2 x ArH), 8.14 (d, 1H, J = 7.9 Hz, ArH), 8.28 (d, 1H, J = 1.5 Hz, ArH), 8.79 (s, 1H, ArH), 8.85 (d, 1H, J = 8.4 Hz, ArH).
MS: 197 (M^+), 180, 152, 125, 29, 18.

Example 2

3-cyano-1-naphthoic acid *via* carbonylation.

Bis(triphenylphosphine)palladium (II) chloride (0.77g) in N-methylpyrrolidinone (170g), (10g), triphenyl phosphine (0.57g), and triethylamine (11g,) are mixed in a nitrogen inerted pressure vessel (Parr reactor) at ambient temperature. Water (15.5g) is added and the reactor is repeatedly purged with argon to remove residual air or oxygen. The reactor is vented and then pressurised with carbon monoxide to 7 bar absolute pressure (6 bar gauge pressure) and the mixture stirred at 85 C for 10 hours, maintaining carbon monoxide pressure within the reactor at 6 barg. The mixture is cooled to 50 C and vented to atmospheric pressure, and the reaction mixture then filtered through a bed of celite to remove solids. The filter cake is washed with toluene (160.5g) and then with water (124g). The combined filtrates and washes are allowed to settle and the lower aqueous layer separated. The toluene layer is extracted with water (2 x 124 g). The combined aqueous phase and aqueous extracts were washed with toluene (120g), 2M hydrochloric acid (64.5 ml) are added to the aqueous solution over 30 minutes with stirring at 25 to 30 C. The organic layer is separated off and retained, the aqueous layer is extracted with toluene (2 x 120g). The combined organic layer and toluene extracts are mixed with water (62g) and 2M sodium hydroxide solution (16.2ml) to extract the product into the aqueous phase. The organic phase is extracted with further water (62g) plus 2M sodium hydroxide solution (16.2ml). The combined aqueous extracts are mixed with dichloromethane (350g) and the

mixture acidified by addition of 2M hydrochloric acid (43ml) over 30 minutes at 25 to 30 C. The lower organic phase is separated and retained, the aqueous phase is extracted with further dichloromethane (100g). The combined dichloromethane solution and extract are washed with 2M hydrochloric acid (21.5ml), toluene (120g) is added and dichloromethane is removed by evaporation under reduced pressure to leave a toluene solution of the product. This solution is heated to 60 C, *iso*-hexane (300g) is added over 30 minutes at 60 C, and the mixture cooled over 3 hours to 5 C so as to crystallise the product, which is isolated by filtration. The product is washed with pre-cooled *iso*-hexane at 0 C to 5 C and it is then dried overnight in a vacuum oven at 40 C (5.66 g, 65% yield).

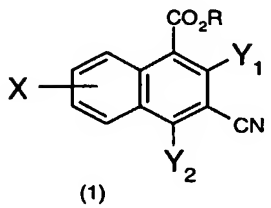
The obtained product is confirmed by analysis to be the same as in Example 1.

CONCLUSIONS

The new routes described herein offer significantly improved means for large scale manufacture of naphthalene cyanoacid (1) compared with methodology available from the chemical literature. These new routes offer advantage in terms of significantly improved through-route yield (with considerable potential for yet further yield improvement), they avoid the large scale process operability difficulties associated with the previous literature chemistry, they give product of lower cost of manufacture and they avoid the effluent toxicity and reagent toxicity associated with use of stoichiometric mercury salts specified in the previously published chemistry to such products.

CLAIMS

1. A process for preparing the compound of formula (1)

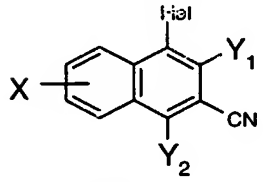


(1)

wherein X and/or Y_1 and/or Y_2 are independently H, cyano, nitro, trifluoromethoxy, trifluoromethyl, alkoxy, or alkyl and R is H or alkyl

either

a) in the case where R=H, by metallo-dehalogenation followed by carboxylation of a compound of formula (12)

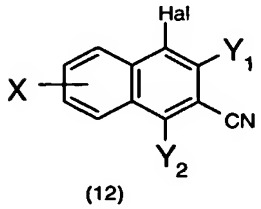


(12)

wherein X, Y_1 and Y_2 are as defined above, and Hal is Br, I or Cl

or

b) (in the case where R=H or alkyl) by palladium mediated carbonylation of a compound of formula (12)

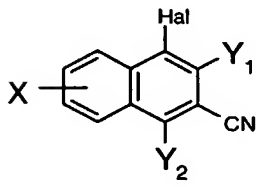


(12)

with the proviso that the compound 1-iodo-3-cyano-2-methoxynaphthalene is excluded, followed by solvolysis.

2. A process for preparing the compound of formula (1) according to claim 1 characterized in that step a) is carried out by treatment of the compound of formula (12) with an alkyl-lithium reagent followed by reaction of the lithiated intermediate with carbon dioxide and then acidification.

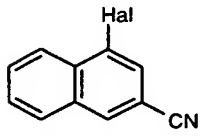
3. The compound of formula (12)



(12)

wherein X and/or Y_1 and/or Y_2 are independently H, cyano, nitro, trifluoromethoxy, trifluoromethyl, alkoxy, or alkyl and Hal is Br, I or Cl, with the proviso that the compounds 1-iodo-3-cyano-2-methoxynaphthalene and 1-chloro-3-cyano-2-methoxynaphthalene are excluded.

4. A process for preparing a compound of formula (12, $Y_1=Y_2=X=H$)



(12, $Y_1=Y_2=X=H$)

wherein Hal is Br, I or Cl

(i) by

(a) treating malic acid (7) with oleum or alternative strongly acid dehydrating media to give coumalic acid (8);

(b) esterifying coumalic acid (8) to give a pyrone ester (9);

(c) brominating the pyrone ester (9) to give a 3-bromo coumalic ester (10);

(d) reacting the 3-bromo coumalic ester (10) with *in situ* generated benzyne followed by decarboxylation to give a bromonaphthoate (11); and

(e) converting/transforming bromonaphthoate (11) to 1-bromo-3-cyano naphthalene (12, $Y_1=Y_2=X=H$)

(ii)

by

(a) treating malic acid (7) with oleum or alternative strongly acid dehydrating media to give coumalic acid (8);

(b) converting coumalic acid (8) into coumalonitrile (25) and subsequently brominating to give 3-bromo-5-coumalonitrile (27); and then

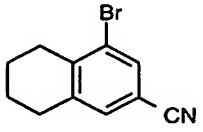
(c) converting 3-bromo-5-coumalonitrile (27) into 1-bromo-3-cyano naphthalene (12, $Y_1=Y_2=X=H$)

by cycloaddition of *in situ* generated benzyne, followed by subsequent decarboxylation

or (iii)

by

1a) cyanation of 1,2,3,4-tetrahydronaphthalene followed by bromination to give compound (63)



(63)

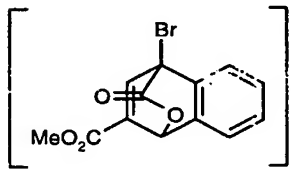
or

1b) bromination of 1,2,3,4-tetrahydronaphthalene followed by cyanodebromination, followed by bromination to give the compound of formula (63); or

1c) bromination of 1,2,3,4-tetrahydronaphthalene followed by carboxylation followed by conversion to the 6-cyano-1,2,3,4-tetrahydronaphthalene followed by bromination to give compound (63); followed by

2) oxidative aromatization of compound (63) into 1-bromo-3-cyano naphthalene (12, $Y_1=Y_2=X=H$).

5. A process according to claim 4characterized in that in process (i) step (d) is carried out by reacting a 3-bromo coumalic ester(10) with *in situ* generated benzyne to give an intermediate (15)

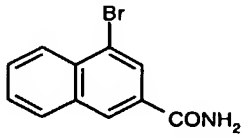


(15)

followed by decarboxylation to give a bromonaphthoate (11).

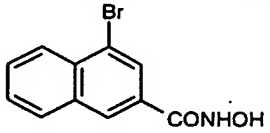
6. A process according to claim 4 characterized in that in process (i) step (e) is carried out by either

e1) reaction of compound (11) with ammonia to give compound (18)



followed by dehydration to give compound (12);

e2) reaction of compound (11) with hydroxylamin or a salt thereof to give compound (20);

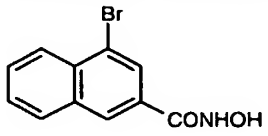


followed by dehydration to give compound (12);

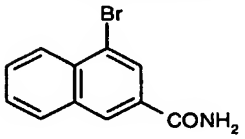
or

e3) direct conversion of compound (11) to compound (12).

7. The compound of formula (20)

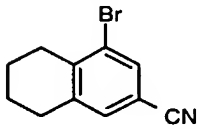


8. The compound of formula (18)



9. 3-bromo-5-coumalonitrile (27)

10. The compound of formula (63)



(63)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 03/01045

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: C07C 253/00, C07C 255/57, C07C 255/52, C07C 233/67, C07C 233/65, C07D 309/38

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-INTERNAL, WPI DATA, CHEM. ABS DATA, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	J. Med. Chem., Vol 45, no. 18, 2002, Jeffrey S. Albert et al: "Design, Synthesis, and SAR of Tachykinin Antagonists: Modulation of Balance in NK1/NK2 Receptor Antagonist Activity", page 3972 - page 3983; page 3973, Scheme 2; page 3980 - page 3981, nos. 18-20 --	1,3
A	WO 0177069 A1 (ASTRAZENECA AB), 18 October 2001 (18.10.01), page 15, line 19 - page 16, line 14 --	1,3
A	WO 0059873 A1 (ASTRAZENECA AB), 12 October 2000 (12.10.00), page 13, line 19 - page 14, line 15 --	1,3

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
10 October 2003	14 -10- 2003
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Gerd Strandell/EÖ Telephone No. +46 8 782 25 00

Form PCT/ISA/210 (second sheet) (July 1998)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 03/01045

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 0020003 A1 (ZENECA LIMITED), 13 April 2000 (13.04.00), page 21, line 29 - page 22, line 26	1,3
A	WO 0020389 A1 (ZENECA LIMITED), 13 April 2000 (13.04.00), page 24, line 25 - page 25, line 23	1,3
A	WO 0212168 A1 (ASTRAZENECA AB), 14 February 2002 (14.02.02), page 16, line 20 - page 17, line 17	1,3
A	WO 0177089 A1 (ASTRAZENECA AB), 18 October 2001 (18.10.01), page 29, line 20 - page 30; page 32, line 11 - page 34, line 6	1,3
A	STN International, File CASREACT, Accession no. 44:10012, Richtzenhain, Hermann et al: "Substitution reactions with metalloorganic compounds. IV. The Grignardization of methoxyl-containing aromatic nitriles"; & Chem. Ber. (1949), 82, 408-17	3,7,8
A	WO 8906645 A1 (ABBOTT LABORATORIES), 27 July 1989 (27.07.89), page 10; page 34, Example 52	10
A	US 2948724 A (MELVILLE SAHYUN ET AL), 9 August 1960 (09.08.60), column 1, line 60 - column 2, line 57; column 11, line 38 - line 55	4,6-8,10
A	Journal of the American Chemical Society, Vol. 97, no. 8, April 1975, W. Adcock et al: "Substituent Effects. XII.1 Substituent Effects by 19F NMR", page 2198 - page 2205	10

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE03/01045

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see next sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-8, 10

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

According to Article 34 (3) (a-c) and Rule 13.2, an international application shall relate to one invention only or to a group of inventions linked by one or more of the same or corresponding "special technical features", i.e. features that define a contribution which each of the inventions makes over the prior art. In order to fulfil the requirements of unity of invention, it is necessary that the intermediate compounds are closely interconnected with the end products as well as with themselves. Such close connection requires that the essential structural part of the end product is incorporated by the intermediate. However, the present application lacks a single general inventive concept based on the above principle. This leads to the presence of the subjects listed below, each falling under its own restricted inventive concept.

1. Claims 1-8 and 10. Process for preparing compounds of formula (I), intermediates of formula (12) and preparation thereof, intermediates of formulae (20), (18) and (63).

2. Claim 9. Intermediate of formula (27).

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 03/01045

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0177069 A1	18/10/01	AU 4499901 A	23/10/01
		EP 1278719 A	29/01/03
		GB 0009457 D	00/00/00
		US 2003158180 A	21/08/03
		GB 0009456 D	00/00/00
WO 0059873 A1	12/10/00	AU 3569200 A	23/10/00
		BG 106074 A	31/05/02
		BR 0009582 A	26/12/01
		CA 2368240 A	12/10/00
		CN 1345307 T	17/04/02
		CZ 20013574 A	15/05/02
		EE 200100520 A	16/12/02
		EP 1169302 A	09/01/02
		GB 9907571 D	00/00/00
		HU 0200707 A	29/06/02
		IL 145645 D	00/00/00
		JP 2002541137 T	03/12/02
		NO 20014855 A	06/12/01
		PL 350568 A	16/12/02
		SK 13012001 A	04/04/02
		TR 200102875 T	00/00/00
		US 6476077 B	05/11/02
		US 6586432 B	01/07/03
		US 2003092713 A	15/05/03
WO 0020003 A1	13/04/00	AT 230598 T	15/01/03
		AU 4637899 A	01/02/00
		AU 6111099 A	26/04/00
		BR 9912013 A	10/04/01
		BR 9914333 A	26/06/01
		CA 2336806 A	20/01/00
		CA 2344807 A	13/04/00
		CN 1309638 T	22/08/01
		CN 1322134 T	14/11/01
		DE 69904847 D	00/00/00
		EP 1097137 A	09/05/01
		EP 1119355 A,B	01/08/01
		SE 1119355 T3	
		GB 9821703 D	00/00/00
		GB 9914886 D	00/00/00
		GB 9922519 D	00/00/00
		IL 140770 D	00/00/00
		IL 142048 D	00/00/00
		JP 2002520316 T	09/07/02
		JP 2002526410 T	20/08/02
		NO 20010151 A	05/03/01
		NO 20011766 A	05/06/01
		US 6365602 B	02/04/02
		US 6500818 B	31/12/02
		WO 0002859 A	20/01/00
		ZA 200102658 A	01/07/02
		GB 9905238 D	00/00/00

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 03/01045

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0020389 A1	13/04/00	AU 4637899 A	01/02/00
		AU 6111199 A	26/04/00
		BR 9912013 A	10/04/01
		BR 9915904 A	21/08/01
		CA 2336806 A	20/01/00
		CA 2345133 A	13/04/00
		CN 1309638 T	22/08/01
		CN 1322196 T	14/11/01
		EP 1097137 A	09/05/01
		EP 1119551 A	01/08/01
		GB 9821699 D	00/00/00
		GB 9914886 D	00/00/00
		GB 9922521 D	00/00/00
		IL 140770 D	00/00/00
		IL 142045 D	00/00/00
		JP 2002520316 T	09/07/02
		JP 2002526527 T	20/08/02
		NO 20010151 A	05/03/01
		NO 20011765 A	07/06/01
		US 6365602 B	02/04/02
		WO 0002859 A	20/01/00
		ZA 200102651 A	01/07/02
		GB 9906278 D	00/00/00
		GB 9909839 D	00/00/00
WO 0212168 A1	14/02/02	AU 8456801 A	18/02/02
		BR 0112957 A	08/07/03
		CA 2415467 A	14/02/02
		EP 1307425 A	07/05/03
		GB 0019008 D	00/00/00
		NO 20030509 A	24/03/03
WO 0177089 A1	18/10/01	AU 4699901 A	23/10/01
		EP 1276729 A	22/01/03
		GB 0008728 D	00/00/00
		GB 0008727 D	00/00/00

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 03/01045

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 8906645 A1	27/07/89	CA 1337425 A,C	24/10/95
		DE 68909253 D,T	24/02/94
		EP 0325963 A,B	02/08/89
		SE 0325963 T3	
		EP 0395734 A	07/11/90
		ES 2059570 T	16/11/94
		JP 2693843 B	24/12/97
		JP 4500356 T	23/01/92
		MX 9203464 A	01/09/92
		US 5086074 A	04/02/92
		US 5128362 A	07/07/92
		US 5140040 A	18/08/92
US 2948724 A	09/08/60	NONE	

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY
(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

REC'D 24 MAR 2004
WIPO PCT

Applicant's or agent's file reference	FOR FURTHER ACTION See Form PCT/IPEA/416	
100712-1 WO		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/SE 2003/001045	18.06.2003	20.06.2002

International Patent Classification (IPC) or national classification and IPC
C07C 253/00, C07C 255/57, C07C 255/52, C07C 233/67, C07C 233/65, C07D 309/38

Applicant
AstraZeneca AB et al

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 5 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:

a. ☐ *(sent to the applicant and to the International Bureau)* a total of _____ sheets, as follows:

☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).

☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.

b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s))
_____, containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

- ☒ Box No. I Basis of the report
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

Date of submission of the demand	Date of completion of this report
22.12.2003	11.02.2004
Name and mailing address of the IPEA/SE Patent- och registreringsverket Box 5055 S-102 42 STOCKHOLM Facsimile No. +46 8 667 72 88	Authorized officer Gerd Strandell/ELY Telephone No. +46 8 782 25 00

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/SE 2003/001045

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ This report is based on a translation from the original language into the following language _____, which is the language of a translation furnished for the purposes of:

☐ international search (under Rules 12.3 and 23.1(b))
☐ publication of the international application (under Rule 12.4)
☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report):*

☒ the international application as originally filed/furnished

☐ the description:

pages _____ as originally filed/furnished
pages* _____ received by this Authority on _____
pages* _____ received by this Authority on _____

☐ the claims:

pages _____ as originally filed/furnished
pages* _____ as amended (together with any statement) under Article 19
pages* _____ received by this Authority on _____
pages* _____ received by this Authority on _____

☐ the drawings:

pages _____ as originally filed/furnished
pages* _____ received by this Authority on _____
pages* _____ received by this Authority on _____

☐ a sequence listing and/or any related table(s) – see Supplemental Box Relating to Sequence Listing.

3. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages _____
☐ the claims, Nos. _____
☐ the drawings, sheets/figs _____
☐ the sequence listing *(specify)*: _____
☐ any table(s) related to the sequence listing *(specify)*: _____

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

☐ the description, pages _____
☐ the claims, Nos. _____
☐ the drawings, sheets/figs _____
☐ the sequence listing *(specify)*: _____
☐ any table(s) related to the sequence listing *(specify)*: _____

* *If item 4 applies, some or all of those sheets may be marked "superseded."*

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/SE 2003/001045

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application

☒ claims Nos. 9

because:

☐ the said international application, or the said claims Nos. _____
relate to the following subject matter which does not require an international preliminary examination *(specify)*:

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. _____
are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. _____ are so inadequately supported
by the description that no meaningful opinion could be formed.

☒ no international search report has been established for said claims Nos. 9

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form
☐ has not been furnished
☐ does not comply with the standard

the computer readable form
☐ has not been furnished
☐ does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in the Annex C-*bis* of the Administrative Instructions.

☐ See Supplemental Box for further details.

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/SE 2003/001045

Box No. IV Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees the applicant has:

☐ restricted the claims.

☐ paid additional fees.

☐ paid additional fees under protest.

☐ neither restricted nor paid additional fees.

2. ☒ This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is:

☐ complied with.

☒ not complied with for the following reasons:

According to Rules 13.1, 13.2 and 13.3 an international application shall relate to one invention only or to a group of inventions linked by one or more of the same or corresponding "special technical features", i.e. features that define a contribution which each of the inventions makes over the prior art. In order to fulfil the requirements of unity of invention, it is necessary that the intermediate compounds are closely interconnected with the end products as well as with themselves. Such close connection requires that the essential structural part of the end product is incorporated by the intermediate. However, the present application lacks a single general inventive concept based on the above principle. This leads to the presence of the subjects listed below, each falling under its own restricted inventive concept.

1. Claims 1-8 and 10. Process for preparing compounds of formula (I), intermediates of formula (12) and preparation thereof, intermediates of formulae (20), (18) and (63).

2. Claim 9. Intermediate of formula (27).

4. Consequently, this report has been established in respect of the following parts of the international application:

☐ all parts.

☒ the parts relating to claims Nos. 1-8, 10

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/SE 2003/001045

Box No. V **Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Claims	1-8, 10	YES
	Claims		NO
Inventive step (IS)	Claims	1-8, 10	YES
	Claims		NO
Industrial applicability (IA)	Claims	1-8, 10	YES
	Claims		NO

2. Citations and explanations (Rule 70.7)

The opinion given is based on what is searched. Confer Box No. III and Box No. IV in this report and PCT Rule 66.1(e).

Documents cited in the International Search Report:

D1: J. Med. Chem., Vol 45, no. 18, 2002, Jeffrey S. Albert et al: "Design, Synthesis, and SAR of Tachykinin Antagonists: Modulation of Balance in NK1/NK2 Receptor Antagonist Activity", page 3972 - page 3983; page 3973, Scheme 2; page 3980 - page 3981, nos. 18-20

D2: WO 0177069 A1 (ASTRAZENECA AB), 18 October 2001 (18.10.01), page 15, line 19 - page 16, line 14

D3: WO 0059873 A1 (ASTRAZENECA AB), 12 October 2000 (12.10.00), page 13, line 19 - page 14, line 15

The cited documents represent the general state of the art. The invention defined in claims 1-8 and 10 is not disclosed by any of these documents.
The cited prior art does not give any indication that would lead a person skilled in the art to the claimed process for the preparation of 3-cyano-1-naphthoic acid and some analogues thereof, the intermediate 1-halo-3-cyano naphthalene and some analogues thereof used in this process and a process for the preparation of said intermediate. Therefore, the claimed invention is not obvious to a person skilled in the art.
Accordingly, the invention defined in claims 1-8 and 10 is novel and is considered to involve an inventive step. The invention is industrially applicable.